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Enthesopathy of rheumatoid and ankylosing spondylitis

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The invitation to speak before the Heberden Society on this annual occasion is a great honour. For me it was also a stimulus to assemble some thoughts and observations on spondylitis—a subject in which my colleagues and I have been interested for some time.

It has always seemed to me very odd that whilst rheumatoid arthritis (RA) and ankylosing spondylitis (AS) can be distinguished on clinical, epidemiological, genetic, immunological, and even therapeutic grounds, an acceptable pathological differentiation has yet to emerge. Indeed, histological studies often emphasize the similarities rather than explain the differences. The synovial reaction appears to be the same in both (Julkunen, 1966); and Cruickshank (1951) has said that one can match all stages in diarthrodial joints in RA and AS, which is to an extent true but nevertheless does not help us to understand, for instance, the obvious difference in the behaviour of the diarthrodial sacroiliac joints. We have also been repeatedly told (Güntz, 1933; Freund, 1942; Geiler, 1969) that spinal apophyseal arthritis is common to both; but the mechanisms responsible for the differential susceptibility of these joints to ankylosis remains obscure. And if, as Engfeldt, Romanus, and Ydén (1954) and Bywaters (1967, 1969) have indicated, ossification of intervertebral discs in AS is inflammatory in origin, we may ask why similar lesions do not occur in rheumatoid spondylitis (RS). Thus, we seem to lack a clear morphological explanation for the obvious differences in the evolution of the two main forms of spondylitis: RS is characterized by instability, AS by progressive ossification.

In an attempt to gain some insight into this problem of the differential pathology, I shall first discuss the nature of RS and then consider the morphogenesis of progressive ossification in AS. What I have to say is largely based on a personal study of *post-mortem* material, and a small but important group of biopsy specimens in AS. Table I shows the total number of necropsies in RA and AS and the number of cases in each group in which various parts of the axial skeleton have been examined; and secondly the origin and number of biopsy specimens in AS.

Table I *Material available for study*

Source of material	*Diagnosis*	*Total cases*	*Material*							
			Spine					*Sacroiliac joints*	*Manubrio-sternal joints*	
			Cervical	*Thoracic*	*Lumbar*					
Necropsy	AS	13	10	5	9			8	8	
	RA	119	55	4	13			7	17	
Biopsy	AS	13		Ligamentous attachments	5	Iliac crest	3			
						Greater trochanter	1			
						Patella	1			
				Capsular ligaments	4	Knee	4			
				Intevertebral discs	4	Thoracic	1			
						Lumbar	3			

I will begin with a few words about ligamentous attachments since they figure prominently in the discussion and have generally received less attention than most other articular components. A ligamentous attachment to bone—an enthesis—presents a characteristic structural sequence. Just before reaching the bone the fibre bundles of the ligament become more compact, then cartilaginous and then calcified before being joined to the bone by a cement line (Plate 1(*a*)). An abnormality in this area may be called an enthesopathy—a word I first met in a publication by our colleagues in Piestany (Niepel, Kostka, Kopecky, and Manca 1966). The cartilaginous zone may be prominent or inconspicuous, and there is considerable variation in the depth of the calcified zone. Capillary-like vessels may be seen close to the bone and in some sites may pass through the enthesis to the marrow or to haversian canals. Histologically the vessels seem to be very scanty, but the studies of Peacock (1959) with labelled phosphorus and the injected specimens of Rathbun and Macnab (1970) indicate that the potential vascular bed is larger than histological sections suggest. The annulus fibrosus of the intervertebral disc is a notable exception to the rule, for it is generally held that all but its outer fibres are avascular. Little is known of the metabolism of an enthesis, and even less of its biochemistry. However, it is evident from the ultrastructural studies of Cooper and Misol (1970) that the cells in both calcified and uncalcified zones are viable. Moreover, the late Professor D. V. Davies showed many years ago that in immature animals injected with labelled sulphate radioactivity was greater at the osseous attachment than elsewhere in a ligament (Davies and Young, 1954). I have observed a similar localization in young rats injected with radioactive calcium instead of labelled sulphate, the label in this case being especially concentrated in a narrow band, probably at the junction of the calcified and uncalcified zones (Plate 1(*b*)). It would seem therefore that an enthesis is a metabolically active site, at least during growth—a point of possible significance since AS often begins in adolescence and early adult life (Wood, 1968), and as I hope to show, involves ligamentous attachments.

Rheumatoid spondylitis (RS)

It has recently become widely recognized that spondylitis in RA is a common cause of disability which manifests itself mainly in the cervical region in the form of instability and sometimes severe dislocation (Ball and Sharp, 1971). Cervical instability and dislocation are associated with erosive arthritis of the apophyseal joints, and destructive lesions of the corresponding disc. But whereas apophyseal arthritis may occur at any level in the spine, dislocation is virtually confined to the cervical region. Thus, to begin to understand the pathogenesis of RS, we need to explain the origin and localization of the cervical disc lesion, and the nature of the thoracic and lumbar disc lesions that are occasionally seen. These problems were initially approached by examining fourteen rheumatoid cervical spines in which there was little or no radiological evidence of disease along with twelve non-arthritic controls (Ball, 1958). In all but one of the rheumatoid cases small macroscopic reddish lesions were found in one or more discs but not in the common ligaments or ligamenta flava. The lesions were always most pronounced in the lateral margins of the disc, and in some cases were confined to this region. (Similar lesions were not observed in subsequent studies of four cases of AS in which there was little or no radiological evidence of disease.) Histologically, these disc lesions were found to be related to neurocentral (NC) joints (Fig. 1A and B). NC joints are formed by a cleft in the lateral margin of the disc which lies between the lower lateral border of the vertebral body above and the NC lip of the subjacent vertebra. The cleft is covered laterally by a fibrous membrane lined by synovium. According to Ecklin (1960), NC joints are not present at birth and their appearance depends on the development of the NC lip which is not completed until about the age of 20 years. Like

PLATE 1(*a*) *A healthy enthesis; from below upwards, bone, calcified zone, cartilaginous zone, and compact ligament. Haematoxylin and eosin.* × 150

PLATE 1(*b*) *Autoradiograph of a normal enthesis in a young rat injected with* ^{45}Ca. *Radioactivity (black grains) is concentrated in the enthesis between ligament below and bone above. Toluidine blue.* × 150

PLATE 1(*c*) *Granulation tissue eroding attachment of an alar ligament. Haematoxylin and eosin.* × 60

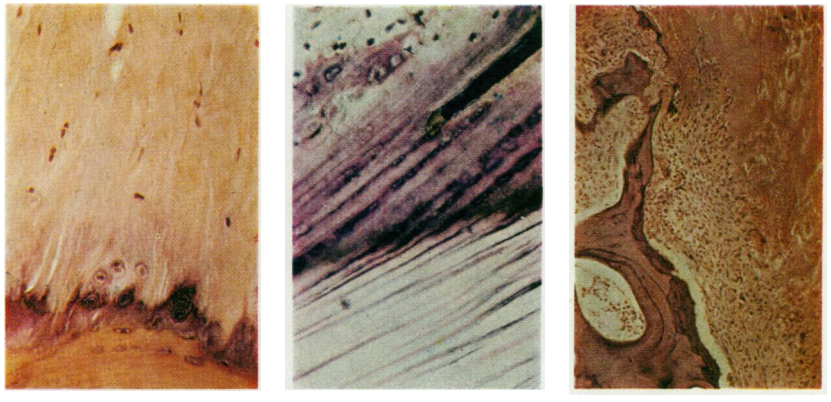
PLATE 1(*d*) *Iliac crest. Inflammatory erosive lesion localized to ligamentous attachment. Haematoxylin and eosin.* × 48

PLATE 1(*e*) *Anterior surface of patella. Inflammatory cells concentrated in centre of erosive lesion of ligamentous attachment. Haematoxylin and eosin.* × 60

PLATE 1(*f*) *Greater trochanter. Lymphocytes, plasma cells, and polymorphonuclear leucocytes in erosive lesion of ligamentous attachment. Haematoxylin and eosin.* × 150

PLATE 1(*g*) *Greater trochanter. Edge of erosive lesion of ligamentous attachment, showing early deposition of reactive bone. Haematoxylin and eosin.* × 24

PLATE 1(*h*) *Greater trochanter. A later stage of healing. Erosion is filled in by trabeculae of reactive bone to which ligament has become reattached in places. Haematoxylin and eosin.* × 60



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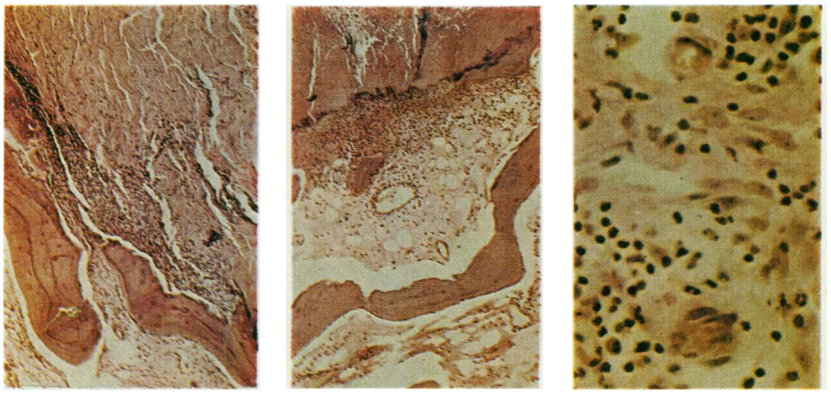
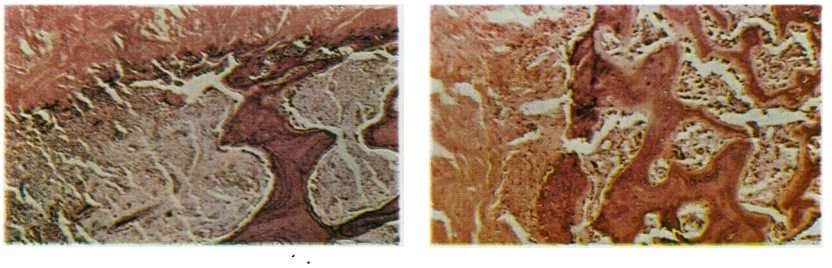


d, e, f



g, h

Plate 1. *a—h.* To face p. 214

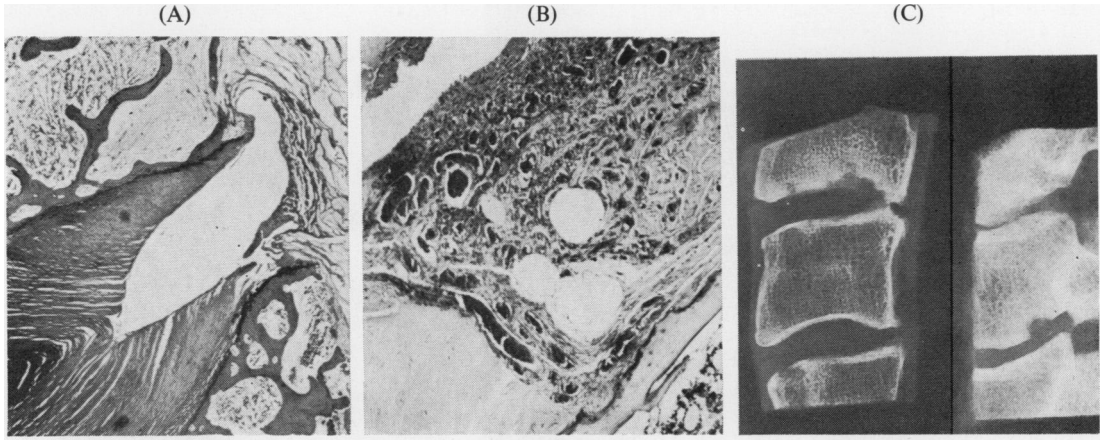


FIG. 1 *Disc lesions in RA*

(A) *Coronal section of NC joint, showing minimal arthritic changes. Haematoxylin and eosin* × 16. *Reproduced from 'Modern Trends in Rheumatology' (1971) p.* 118, *fig.* 1(*c*). *Butterworth, London.*

(B) *Coronal section, showing part of lining of NC joint, and erosion of annulus by granulation tissue. Haematoxylin and eosin* × 52

(C) *Sagittal (left) and coronal (right) sections of same discs showing, respectively, erosions at disc-bone border and at margins of NC joints.*

a bursa, NC joints are more easily recognized when they are inflamed. They then behave like other rheumatoid joints in the sense that the granulation tissue arising in them erodes the neighbouring cartilage and bone with which it comes into contact (Ball, 1968). In the case of NC joints this means erosion of the annulus and its attachments, and to some degree the subjacent bone. The eroding granulation tissue spreads around the disc-bone border gradually replacing the annulus, usually at first posteriorly; and this commonly occurs without conspicuous osteophytosis or other forms of reactive bone deposition (Fig. 1c). The evidence derived from these studies of early cases seems to leave little doubt that the rheumatoid cervical disc lesion is secondary to an erosive process arising in the NC joints. This conclusion enables us to explain both the predominant cervical localization of RS in adults, and the rarity of destructive lesions in cervical discs in juvenile RA (Ansell, 1964). At the same time it implies that the occasional thoracic and lumbar disc lesions seen in RA have a different pathogenesis. This appears to be the case: All subcervical disc lesions I have encountered confirm previous experience (Lawrence, Sharp, Ball, and Bier, 1964) in being attributable to non-specific changes such as disc degeneration, Schmorl's nodes, localized depressed fractures of the vertebral end plates (Fig. 2), or bacterial osteomyelitis.

Atlanto-axial (AA) dislocation can also be ascribed to erosive synovitis which is the earliest lesion detected microscopically at this level. Instability is promoted in various ways, one of which is erosion of ligamentous attachments by granulation tissue arising in neighbouring joints and/or bursae. The AA region, of course, contains numerous synovial structures and the density of synovial tissue relative to bone makes this complex joint unusually susceptible to the effects of erosive synovitis and the associated articular distension and osteoporosis. For instance, severe bone destruction of the upper and apical parts of the dens is commonly found in patients with AA dislocation (Fig. 3). Since the alar ligaments are attached to the apical region of the dens they are frequently affected, and in severe dislocations may become completely detached from the bone (Plate 1(*c*)). Reactive bone formation does not appear to be a prominent feature of these lesions even when some degree of healing by fibrosis has occurred.

The AA region is obviously anatomically exceptional, and I would not like to suggest that the changes which may be encountered in ligamentous attachments in this area can be unreservedly extrapolated to other diarthrodial joints. Nor am I implying that articular instability in general in RA is merely a matter of disorganized ligamentous attachments. The only conclusion I should like to draw at this point is that the enthesopathy of RS, as we have seen it in the annulus fibrosus of cervical discs and in the AA region, is essentially secondary to the effects of synovitis and not associated with prominent reactive bone formation.

Although the rheumatoid cervical spine is inherently unstable, it is known that AA joints and subaxial apophyseal joints may undergo fibrous or bony ankylosis, and that in the final stages apophyseal bony ankylosis in RA and AS may be

FIG. 2 *Lumbar disc lesion in RA due to localized depressed fractures of the end-plates with escape of disc tissue into adjacent vertebrae. Haematoxylin and eosin.* × 3

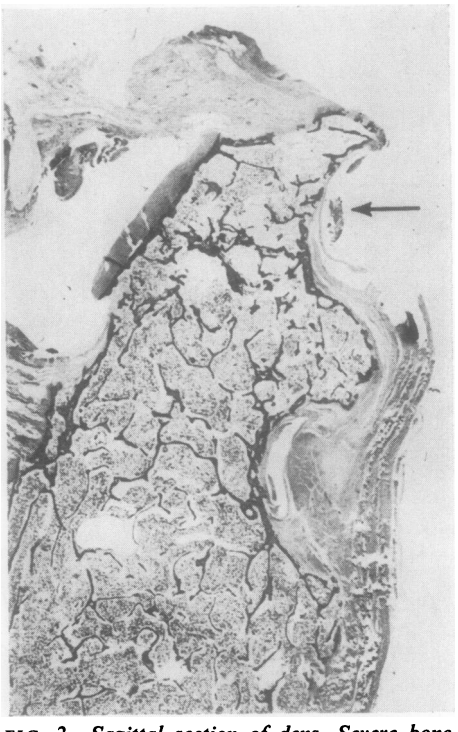


FIG. 3 *Sagittal section of dens. Severe bone erosion of apex and beneath transverse ligament. The upper posterior erosion (arrow) was occupied by a bursa, the outer wall of which was removed during dissection. Haematoxylin and eosin.* × 4

indistinguishable. The possible clinical importance of the natural tendency to stabilization in RA is not within the scope of the present discussion. But there is an aspect of rheumatoid apophyseal ankylosis on which I should like to comment. Occasionally one encounters an apophyseal joint in which the eroded peripheral parts of the articular surfaces are joined by fibrous tissue but in which the central residual articular cartilage is being removed not by granulation tissue but by enchondral ossification. This non-inflammatory process is seen in diverse pathological situations, and normally occurs at growing epiphyseal plates. Briefly, in a joint, it involves penetration of the subchondral plate and calcified cartilage by blood vessels from the marrow and the subsequent deposition of thin layers of bone on the excavated surfaces (Fig. 4). The cartilage ahead of the excavation tends to calcify and the process continues, often in an irregular manner, until finally the whole or the greater part of the articular cartilage is replaced by a rather porous trabecular bone structure. Exactly what triggers off this non-specific mechanism is not fully understood, but immobilization is one obvious possibility. Now enchondral ossification is a prominent feature of some ankylosed apophyseal joints in AS. But as we shall see there is evidence that in this disease apophyseal joints may be immobilized by a mechanism other than fibrous ankylosis.

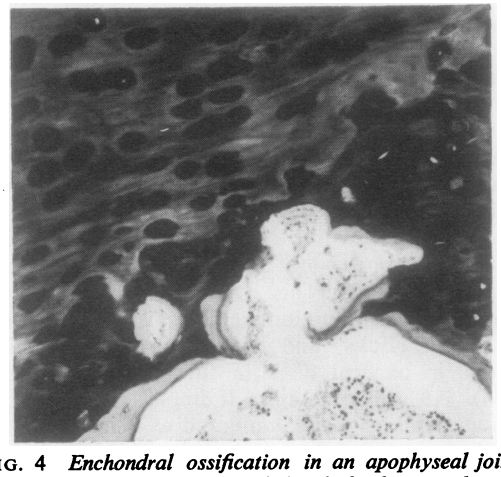


FIG. 4 *Enchondral ossification in an apophyseal joint. There is a breach in the subchondral plate, and parts of the excavation in the cartilage are covered by bone. Haematoxylin and eosin.* × 90

Ankylosing spondylitis (AS)

The age, sex, and duration of disease from the onset of symptoms in the present cases are shown in Table II. None of them is very early in a clinical sense; but this is not as disadvantageous as it may seem. The disease in the spine progresses slowly and intermittently, probably as Dihlmann (1968a, b) suggests

from multiple foci. Hence, many years after the onset some spinal segments may be unaffected while others present various stages in the evolution of the disease.

Table II *Age, sex, and duration of disease in* 13 *cases of AS*

Case No.	*Sex*	*Age (yrs)*	*Duration (yrs)*
1	M	22	4
2	M	32	12
3	M	41	13
4	F	53	14
5	M	45	15
6	M	38	17
7	M	71	20
8	M	46	23
9	M	47	25
10	F	44	28
11	F	56	33
12	M	46	Many
13	M	63	Many

LIGAMENTOUS ATTACHMENTS

While it is necessary to examine the spine, there is another approach to the problem of progressive ossification in AS which has been rather neglected. We can examine biopsy specimens of extraspinal lesions distant from synovial sites such as the well-known tender focal points which occur over the iliac crest and certain other bone surfaces preferably when radiological changes are minimal (Golding, 1936; Guest and Jacobson, 1951). We have carried out elective biopsies of tender areas over the iliac crest in one patient, and over the greater trochanter in another. The changes at the bone surface were similar in both and virtually identical with those found on the anterior surface of the patella in a third patient whose knee had been arthrodesed. In all, active erosive lesions and lesions in various stages of healing were present. In two other patients iliac biopsies were carried out primarily to assess the general bone state. One showed only healed lesions at the bone surface; in the other neither erosive nor healed lesions were found.

In the tender areas at the bone surfaces of the iliac crest, greater trochanter, and patella, the most striking finding was multiple focal microscopic inflammatory lesions localized to the ligamentous attachments, the whole or the greater part of which was destroyed, producing a small erosion or defect in the cortical bone (Plate 1(*d*), (*e*), (*g*)). The number of inflammatory cells in erosive lesions varied considerably even in the same tissue block, suggesting that the inflammatory reaction in the individual lesions at a given site is brief. In some lesions neutrophil polymorphonuclear leucocytes were prominent, but in most, lymphocytes and plasma cells predominated (Plate 1(*f*)). The inflammatory cells, though concentrated in the central part of the erosion, tended to spread along the path of small vessels in the ligament. The marrow spaces in the immediate vicinity of the lesion were oedematous, lacked haemopoetic tissue, and contained scanty plasma cells. In the adipose and loose fibrous tissue adjacent to the ligament, perivenous collections of lymphocytes which probably represent a non-specific reaction to the tissue damage at the attachment were sometimes seen. Preliminary studies indicate that some attachment lesions are related to small vessels perforating the enthesis, but further investigations will be needed to elucidate the pathogenesis. Erosive lesions healed by the deposition of reactive (woven) bone in a finely fibrous connective tissue without preceding cartilage formation. The new bone tended to fill in the cortical defect, joining the deeper bone to the eroded end of the ligament, thus forming a new enthesis above the original level of the cortical surface (Plate 1(*g*), (*h*)). In addition to reactive bone formation, cancellous bone trabeculae beneath the lesion were sometimes thickened by apposition of new lamellar bone. The final stage of healing appeared to be a small irregular bony prominence.

There was some evidence that ligamentous lesions are not confined to the enthesis. In the biopsy specimens of focal tender points in the capsular ligaments of the knee, oedematous foci, sometimes periarteriolar, containing varying numbers of lymphocytes, plasma cells, and polymorphonuclear leucocytes were found (Fig. 5A, overleaf); occasional lesions, however, consisted of focal areas of intense fibroblastic proliferation unaccompanied by reactive bone formation (Fig. 5B). Thus, although ligamentous lesions are probably most commonly located at their attachment to bone, they can occur elsewhere in a ligament; but similar lesions are apparently very rarely seen at other bone surfaces.

DISC LESIONS

If the enthesopathy observed in these extraspinal sites is the hallmark of AS they should be found in both erosive and healing stages in intervertebral discs. Erosive lesions were in fact found in seven otherwise healthy discs from three patients (Cases 1, 2, and 5), four in the lumbar, three in the cervical region. They were not found in the rheumatoid cases or in twelve non-arthritic lumbar spines. The involved segments were not ankylosed by bone posteriorly. A similar erosive disc lesion was found in another patient (Case 11) in whom apophyseal bony ankylosis may have been present. All these erosive lesions were found at the anterior or antero-lateral attachment of the outer annulus at or just below the junction of the annular flange and the

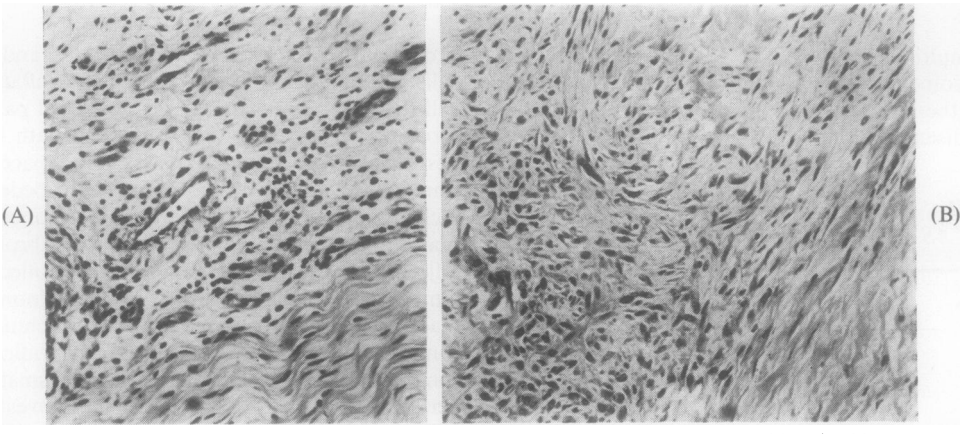


FIG. 5 *Intracapsular ligamentous lesions:* (A) *Oedema and inflammatory cell infiltration.* (B) *Fibroblastic proliferation. Haematoxylin and eosin.* × 150

corner of the vertebral body, sometimes in both sites (Fig. 6 and Plate 2(*a*), (*b*), (*c*), (*d*)). Occasionally, lesions of a similar kind were seen at the posterior attachments of the outer annulus, but the present description is based on lesions at the anterior or antero-lateral attachments. In a given histological section either the upper or the lower attachment was usually involved. Individual lesions sometimes occupied only a small segment of the periphery of the disc and were generally not detected in *post-mortem* radiographs. Lymphocytic and plasma-cell infiltration was scanty in some lesions; in others it was prominent, and in these cases the infiltrating cells tended to spread in a narrow band between the fibres of the outer annulus (Plate 2(*d*), (*e*)). The common ligament was conspicuously unaffected in anterior lesions.

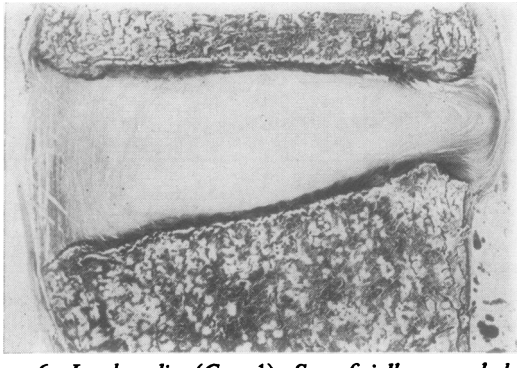


FIG. 6 *Lumbar disc* (*Case* 1). *Superficially normal, but the upper normal and lower abnormal anterior attachments of the outer annulus* (*left*) *are shown in Plate* 2(*a*) *and* (*b*) *respectively. Haematoxylin and eosin.* × 2

As in the extraspinal enthesopathy, the erosive lesion at the attachment of the annulus may heal by reactive bone deposition; and in one of the patients (Case 1) the early stages of this process were observed in a lumbar disc (Plate 2(*f*), (*g*), (*h*)). In precisely the area occupied by erosive lesions, the vertebral cortex just below the annular flange was replaced by a narrow layer of reactive bone which had also spread for a short distance into the outer annulus. The spaces within and immediately beneath the reactive bone layer were devoid of haemopoetic tissue. Near the corner of the vertebral body, part of the eroded annulus remained though new reactive bone could be seen filling in the defect (Plate 2(*g*)). In parts more distant from the disc, the new reactive bone was already joined to the trabeculae of the vertebral body (Plate 2(*h*)). The fate of this new bone, like all reactive bone, is replacement by mature (lamellar) bone by remodelling, thus producing the syndesmophyte composed of mature bone with

PLATE 2(*a*) *Upper normal attachment of outer annulus of disc shown in Fig.* 6. *Haematoxylin and eosin.* × 60

PLATE 2(*b*) *Lower attachment of outer annulus of disc shown in Fig.* 6 *has been destroyed. Lesion active but inflammatory cells scanty. Haematoxylin and eosin.* × 60

PLATE 2(*c*) *Case* 2. *Erosive lesion at attachment of outer annulus in a cervical disc. Haematoxylin and eosin.* × 60

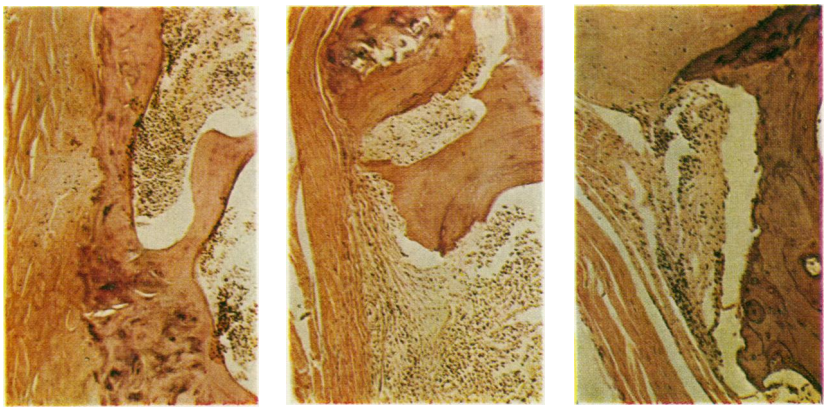
PLATE 2(*d*) *Case* 5. *Lumbar disc. Erosive lesion involving annular flange and attachment of annulus to vertebral body. Inflammatory cells have spread into outer fibres of annulus. Overlying common ligament is healthy. Haematoxylin and eosin.* × 24

PLATE 2(*e*) *Plasma cells and lymphocytes in outer annulus of lesion shown in Plate* 2(*d*). *Haematoxylin and eosin.* × 150

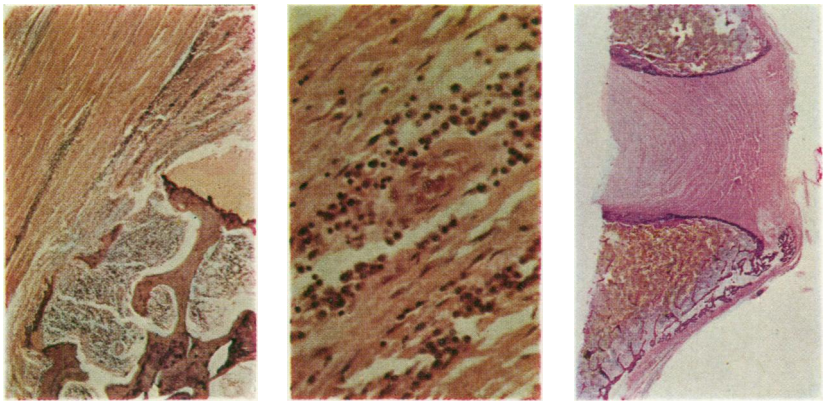
PLATE 2(*f*) *Case* 1. *Lumbar disc. Healing erosive lesion. Upper attachments of the disc are healthy. Cortex of vertebral body just below lower border of disc and nearby outer annulus are replaced by irregular trabeculae of reactive bone. Haematoxylin and eosin.* × 2·5

PLATE 2(*g*) *Upper part of healing lesion in Plate* 2(*f*), *showing eroded edge of annulus and reactive bone filling in the defect. Haematoxylin and eosin.* × 24

PLATE 2(*h*) *Lower part of healing lesion in Plate* 2(*f*), *showing reactive bone joined to normal vertebral trabecular bone* (*lower left*). *Haematoxylin and eosin.* × 60



a, b, c



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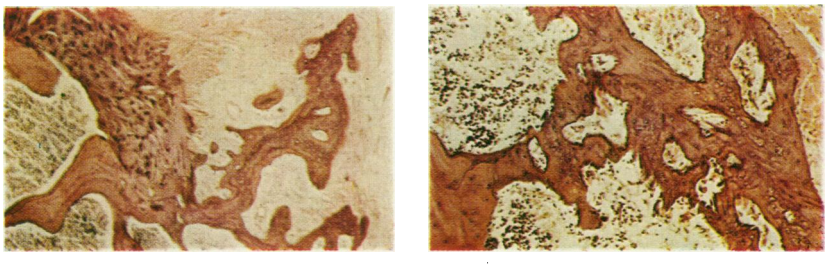


g, h

Plate 2. *a—h.* To face p. 218.

which we are all familiar. Clearly the lower syndesmophyte shown in Fig. 7 springs from the same site as that of the healing erosive lesion. Furthermore, it is composed of mature bone, for the most part firmly attached to the annulus, suggesting that growth has been retarded or halted.

We are so familiar with the fact that syndesmophytes grow across the periphery of the disc that we perhaps forget that some uncertainty exists as to how this happens. François (1965) has suggested that growth may depend on a non-specific process involving progressive chondrification of the annulus; but I have not seen this in the present material and I should like to propose an alternative mechanism. The upper syndesmophyte shown in Fig. 7 is smaller than that on the opposite side of the disc but its base is also composed of mature bone. Its apical parts, however, are ill defined. This apical region consists of reactive trabecular bone and hence is of more recent origin than the base to which it is attached; moreover the apical new bone is apparently repairing an inflammatory erosive lesion involving the edge of the annulus (Plate 3(*a*)).

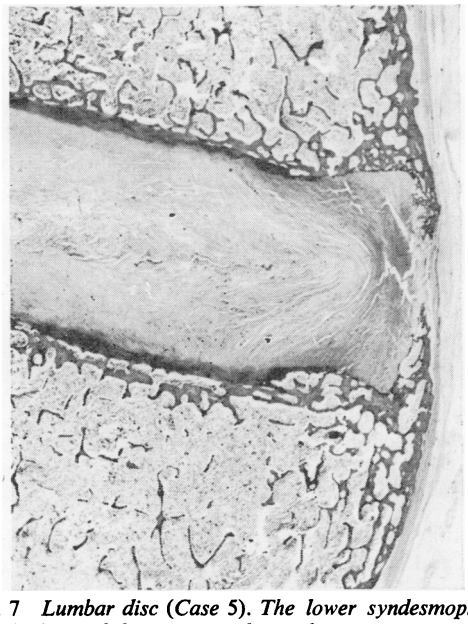


FIG. 7 *Lumbar disc (Case 5). The lower syndesmophyte and the base of the upper syndesmophyte are composed of mature bone. The irregular apical part of the upper syndesmophyte is shown in detail in Plate 3(a). Haematoxylin and eosin.* × 3·5

The tentative interpretation of these findings is that one of the mechanisms by which syndesmophytes grow is the intermittent occurrence of inflammatory lesions in previously stable syndesmophytes. In other words, growth may depend on a recurrence of the lesion by which it was initiated. The completion of the ossific process results in a bony bridge in the outer annulus with resulting ankylosis of the segment. My own observations show that a complete bony bridge can occur in a disc which is otherwise remarkably healthy. Thus one can deduce the various changes that are probably a consequence of ankylosis. These include enchondral ossification of the vertebral end-plates and excessive calcification of the disc (which may produce a spurious radiological narrowing of the disc space or an apparently duplicated end-plate), disc atrophy, and central osteoporosis of the vertebral bodies. Interesting and important as these secondary effects may be, I do not now propose to discuss them further. I would rather consider the pathogenesis of ossification of the apophyseal joints which is more pertinent to my present theme.

APOPHYSEAL ANKYLOSIS

In considering the pathogenesis of apophyseal joint lesions in AS, it seems necessary in the first place to take into account the possibility that ankylosis may in some instances be an entirely non-specific effect of prior ankylosis of the corresponding disc. This suggestion rests mainly on a recent report of Baker, Thomas, and Kirkaldy-Willis (1969) that, in patients with spinal tuberculosis, anterior body fusion is often followed by bony ankylosis of the corresponding apophyseal joints—a phenomenon to which I have previously drawn attention (Ball, 1967). Apophyseal joints are of course rarely if ever themselves involved by tuberculosis. Obviously such a mechanism cannot explain the known occurrence of apophyseal ankylosis in the presence of unankylosed discs (Aufdermaur, 1957). However, it does emphasize the need to interpret spinal lesions in the context of the structural state of all the components of a given segment—a point which seems to be rarely considered in accounts of spinal pathology.

Judging by my own observations and those of others, apophyseal synovitis occurs in both RS and AS (Plate 3(*b*)). In the present material cervical apophyseal erosive synovitis was generally more severe in RA than AS. In the lumbar region erosive synovitis was generally mild in both, though peripheral fibrous ankylosis was observed in some joints in AS. However, in two patients with AS (Cases 1 and 2) pathological changes were noted in lumbar apophyseal joints in non-ankylosed segments which I have not encountered in rheumatoid cases. They consisted of capsular ossification and capsuloligamentous attachment lesions in joints in which fibrous ankylosis was absent, erosive synovitis was minimal or doubtfully present, and the articular cartilages were not degenerate. The earliest lesion (Case 2) (Plate 3(*e* and *f*)) consisted of a small excrescence of reactive bone which separated the

inner capsular attachment from the underlying bone to which in places it was joined; in the spaces between and below the reactive bone there was some oedematous fine connective tissue but no haemopoetic cells, changes indicative of a previous inflammatory reaction. The whole lesion closely resembled the early healing stage of attachment lesions seen elsewhere.

Arising from the opposite inner capsular attachment of the same joint there was a pointed spur of bone which crossed the joint line and almost joined the lesion at the other side (Plate 3(*e*)). Similar lesions were present in the inner capsule of Case 1 (Plate 3(*d*)); and in another lumbar apophyseal joint in this case bony spurs springing from the outer capsule were found (Plate 3(*c*)). The age of both patients, the general appearance of the articular cartilage, and the absence of evidence of trauma in the apophyseal joints or the discs excludes osteoarthritis or joint abuse as the cause of the capsular changes. The simplest interpretation I can put on these capsular findings is that they are the apophyseal equivalent of syndesmophytes. Both Aufdermaur (1954) and Geiler (1969) have described capsular ossification; and Aufdermaur was clearly of the opinion that the process began at the capsular attachments, but did not apparently attach any special significance to this.

Capsulo-ligamentous attachment lesions and the capsular ossification to which they probably give rise could be one of the reasons why apophyseal joints in AS are not infrequently found to consist of a bony shell enclosing well-preserved articular cartilages (Aufdermaur, 1954; Dihlman, 1969). In the present study all stages between this situation and complete synostosis were observed, and at all stages the enclosed articular cartilages were being removed by the non-specific process of enchondral ossification (Fig. 8A and B). There is therefore some evidence that apophyseal ankylosis may at least in some instances be initially produced by a mechanism which originates in capsular attachment lesions similar to those observed at sites distant from synovial tissue, and which results in capsular ossification.

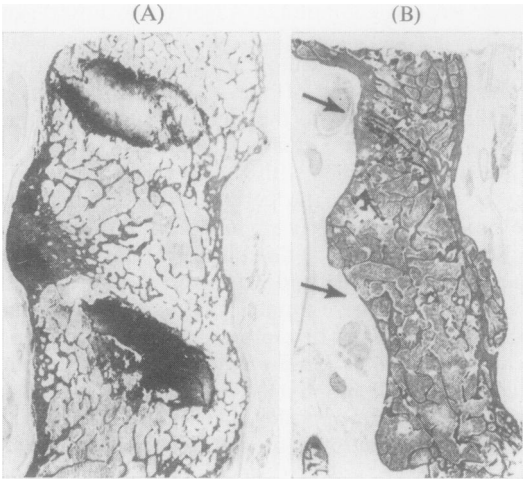


FIG. 8 *Apophyseal ankylosis:* (A) (*Case* 12) *Enchondral ossification of the articular cartilages which are enclosed by a peripheral bony shell. Haematoxylin and eosin.* × 2·3 (B) (*Case* 13) *The upper joint* (*arrow*) *shows a later stage of enchondral ossification; the lower joint* (*arrow*) *shows complete synostosis. Haematoxylin and eosin.* × 1·6

SACROILIAC (SI) JOINTS

While we have this picture of the intermediate stage of apophyseal synostosis in mind I should like to present a section of an SI joint which shows a similar appearance, namely a peripheral shell of bone enclosing articular cartilages showing only evidence of old enchondral ossification (Fig. 9).

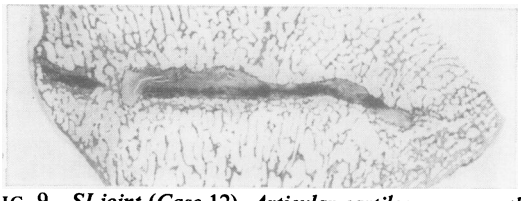


FIG. 9 *SI joint* (*Case* 12). *Articular cartilages are partly replaced by bone. The joint is ankylosed peripherally by bone, thicker anteriorly than posteriorly. Haematoxylin and eosin.* × 1·5

In this case the disease had been present for many years and in other parts of the same joint there was advanced synostosis. But essentially the same

PLATE 3(*a*) *Apical part of the upper syndesmophyte shown in Fig.* 7. *Reactive new bone in an erosive lesion involving the annulus. Haematoxylin and eosin.* × 60

PLATE 3(*b*) *Case* 5. *Marginal erosive arthritis in a lumbar apophyseal joint in AS. Haematoxylin and eosin.* × 60

PLATE 3(*c*) *Case* 1. *Lumbar apophyseal joint, showing bony spurs arising from outer* (*lower*) *capsular attachment. The articular cartilage is healthy; there is minimal inactive synovitis. Haematoxylin and eosin.* × 1·5

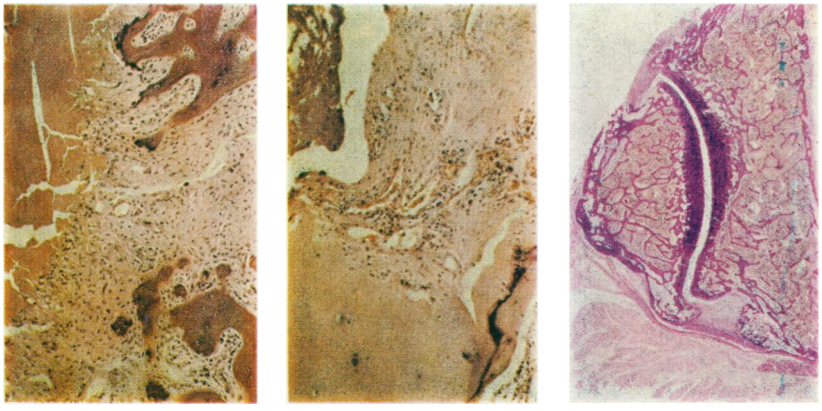
PLATE 3(*d*) *Case* 1. *Another lumbar apophyseal joint, showing a well-developed bony spur in upper part of inner capsule and irregular spicules of bone in lower inner capsular attachment* (*right*). *Haematoxylin and eosin.* × 1·5

PLATE 3(*e*) *Case* 2. *Lumbar apophyseal joint. A bony spur springing from lower left capsular attachment crosses joint line and almost meets a recent healing attachment lesion at opposite side of joint. Haematoxylin and eosin.* × 1·5

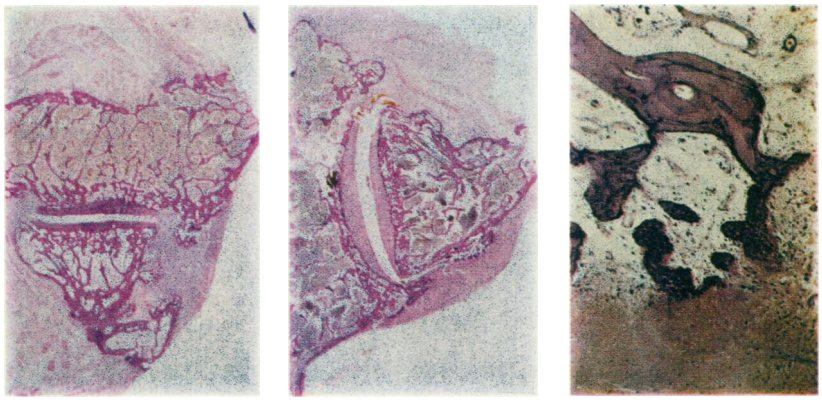
PLATE 3(*f*) *Case* 2. *Edge of healing capsular attachment lesion in Plate* 3(e), *showing reactive bone in cortical defect. In places the new bone has joined up with the eroded ligament. Haematoxylin and eosin.* × 60

PLATE 3(*g*) *Case* 1. *SI joint, showing a thin bar of recently-formed bone crossing periphery of joint. Haematoxylin and eosin.* × 60

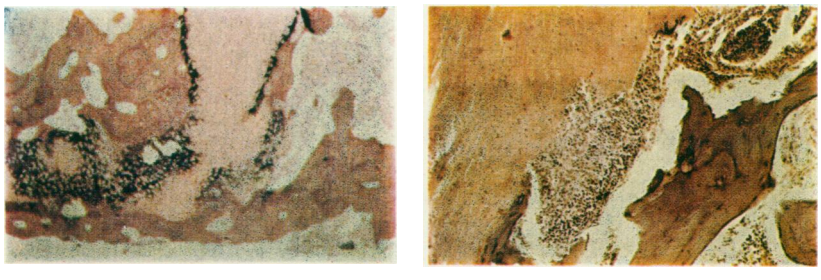
PLATE 3(*h*) *Case* 1. *MS joint. An active erosive lesion at capsular attachment. Haematoxylin and eosin.* × 60



a, b, c



d, e, f



g, h

Plate 3. *a—h.* To face p. 220.

pathology (peripheral bony ankylosis and central enchondral ossification) was found in a patient aged 22 years in whom the duration of disease was only 4 years. A clinical radiograph of this patient taken a few months before death showed the so-called early stages of sacroiliac disease (Fig. 10A). Histological examination of serial slab sections through one of the joints revealed two main features: the joint was ankylosed by bony bridges less than 1 mm. thick, which spanned the periphery of the joint at intervals and were partly composed of woven bone indicative of ossification in fibrous tissue (Plate 3(*g*)); secondly, there was active but irregular enchondral ossification of the articular cartilages especially on the iliac side, where according to Borak (1946) the earliest radiological signs occur (Fig. 10B and Fig. 11).

A comparison of the histology and the radiology of the slab sections of this joint showed that the radiological irregularity of the joint border (the so-called erosions) and the apparent widening can be accounted for by the irregular progression of enchondral ossification, one effect of which, as mentioned above, is the replacement of the subchondral bone plate and the even more densely calcified cartilage by a porous trabecular bone. The bone sclerosis (Fig. 10B) on the iliac side was due mainly to appositional deposition of lamellar bone; on neither side of the joint was there evidence of recent or old osteitis. Perhaps because of the early evolution of the pathological process in the SI joints and the difficulty of obtaining adequate material from earlier cases, we have not seen clear evidence of capsular attachment lesions or synovitis, but otherwise the histology of the SI joint closely resembles that of apophyseal joints. I suspect, therefore, that many of the radiological differences between these diarthrodial joints are more likely to reflect local anatomical factors than differences in the basic pathological mechanisms involved.

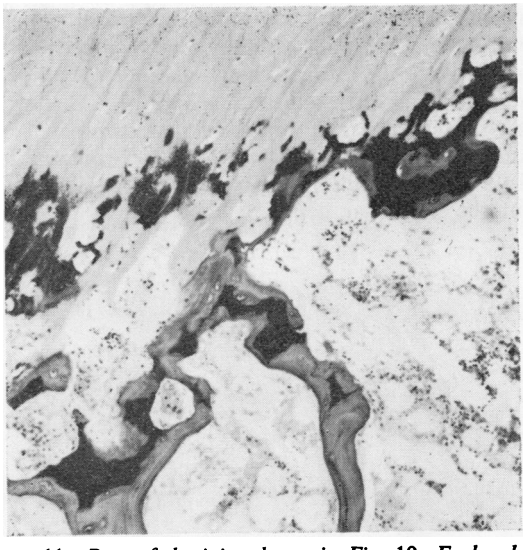


FIG. 11 *Part of the joint shown in Fig.* 10. *Enchondral ossification; fragments of the original articular cartilage have become trapped in advancing trabecular bone formations. Haematoxylin and eosin.* × 90

In contrast to AS, the SI joints in RA were either normal or presented the expected erosive synovitis with or without degrees of osteoarthrosis.

Time does not permit me to discuss the complex pathology of the manubriosternal (MS) joints in RA and AS, but it is germane to my present case to mention that in one of the patients in the AS group both erosive and healing lesions were found at the capsular attachments of the joint which were indistinguishable from those seen in the iliac crest

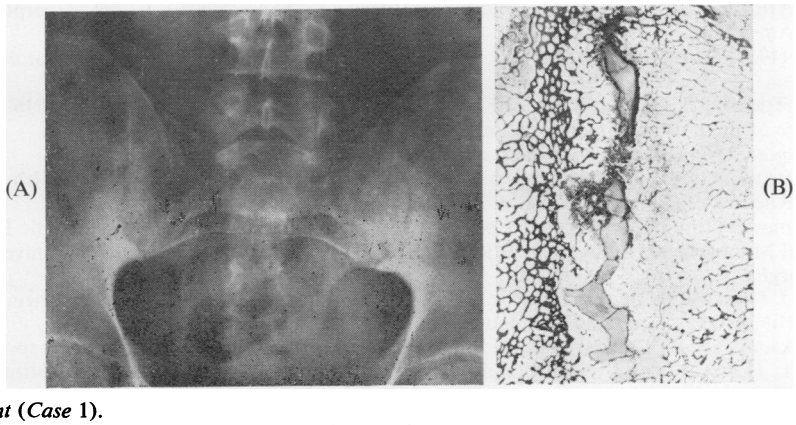


FIG. 10 *SI joint* (*Case* 1).

(A) *Irregularity of joint borders and apparent widening of joint space.*

(B) *Section of central part of joint, iliac side on left. There is irregular enchondral ossification. The zone of sclerosis on the iliac side is in a position judged to be subjacent to the original subchondral plate. There is sacral osteoporosis. Haematoxylin and eosin.* × 1·5

and elsewhere (Plate 3(*h*)); and in another patient with AS the MS joint was ankylosed by a peripheral bony bar, while the cartilaginous plate was undergoing enchondral ossification (Fig. 12). This type of MS ankylosis may represent that considered by Androić, Dürrigl, and Križ (1966) on radiological grounds to be due to primary periosteal ossification; but the bony bar could be described as capsular ossification or perhaps even as a MS syndesmophyte.

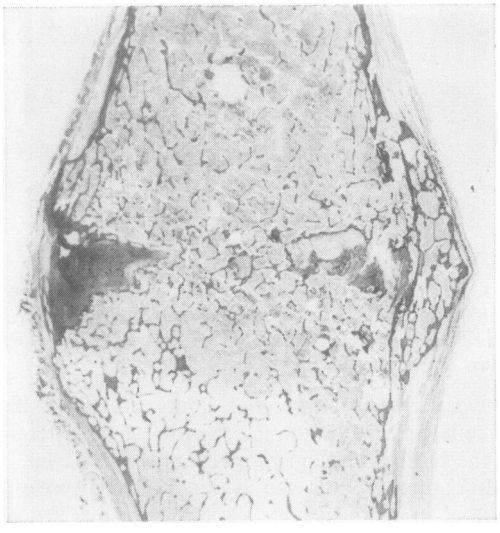


FIG. 12 *MS joint (Case 12). Sagittal section. A shell of mature bone (right) spans the periphery of the joint. Enchondral ossification of the disc is more advanced centrally than peripherally. Haematoxylin and eosin.* × 3

Thus there is evidence in the disc, apophyseal joints, and MS joints that ossification may be initiated and promoted by lesions at ligamentous attachments; and when this peripheral articular process has produced ankylosis, the remainder of the joint is partly or completely replaced by the non-specific mechanism of enchondral ossification.

In conclusion I would suggest that RS is essentially a special case of erosive synovitis. AS also appears to be associated with erosive synovitis, though in general this seems to be less destructive; but in AS there is in addition a striking and possibly unique inflammatory enthesopathy the natural history of which could explain some of the clinical and some of the confusing pathological features of the disease. In emphasizing the relatively minor destructive quality of the inflammatory process in AS, I am not unaware that very rarely these patients develop atlanto-axial dislocation and that occasionally destructive disc lesions occur. This is an aspect of the story of spondylitis which has interested us of late and perhaps we may discuss it on another occasion.

Finally, I am conscious that the evidence I have presented is somewhat fragmentary, as morphological evidence often is, and that some of the fragments may one day be seen to have a different shape. Nevertheless, I do not think we should go amiss to pay a little more attention to that curious structure, the enthesis. As Heberden (1806) said in another connection, ". . . the name of it is met with in very few books".

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